09/827,110

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 41	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 43	Feb 13	CANCERLIT is no longer being updated

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a,

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                CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
                AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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  NEWS INTER    General Internet Information
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  NEWS WWW      CAS World Wide Web Site (general information)

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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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FILE 'MEDLINE' ENTERED AT 13:00:44 ON 14 FEB 2003

=> s sonic hedgehog
L1         2921 SONIC HEDGEHOG

=> s topical
L2       108710 TOPICAL

=> s epithelial
L3       351201 EPITHELIAL

=> s l1 and l2 and l3
L4             2 L1 AND L2 AND L3

=> d l4 1-2

L4   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
AN   2000:227528  CAPLUS
DN   132:270066
TI   Hedgehog and patched antagonists for inhibiting cell and tissue growth and
     differentiation and uses thereof
IN   Burkly, Linda; Wang, Li Chun
PA   Biogen, Inc., USA
SO   PCT Int. Appl., 55 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
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PI WO 2000018428 A2 20000406 WO 1999-US20852 19990910
WO 2000018428 A3 20000525
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
CA 2343335 AA 20000406 CA 1999-2343335 19990910
AU 9959186 A1 20000417 AU 1999-59186 19990910
EP 1112087 A2 20010704 EP 1999-946873 19990910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
US 2002015702 A1 20020207 US 2001-804490 20010312
PRAI US 1998-100037P P 19980911
WO 1999-US20852 W 19990910

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
AN 1999:282115 CAPLUS
DN 130:320865
TI Regulation of **epithelial** tissue by hedgehog-like polypeptides for stimulation of skin or hair formation
IN Wang, Elizabeth A.
PA Ontogeny, Inc., USA
SO PCT Int. Appl., 146 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920298	A1	19990429	WO 1998-US22227	19981020
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002151460	A1	20021017	US 1998-151999	19980911
CA 2307322	AA	19990429	CA 1998-2307322	19981020
AU 9911089	A1	19990510	AU 1999-11089	19981020
EP 1028741	A1	20000823	EP 1998-953814	19981020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001520202	T2	20011030	JP 2000-516694	19981020
PRAI US 1997-955552	A	19971020		
US 1998-151999	A	19980911		
WO 1998-US22227	W	19981020		

OS MARPAT 130:320865
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d que
L1          57 SEA SONIC(2A) HEDGE?(5A)(POLYPEP? OR PEPTID?)
L2          27 DUP REM L1 (30 DUPLICATES REMOVED)
L3        1887 SEA SONIC(2A) HEDGE?(5A)(POLYPEP? OR PEPTID? OR PROTEIN?)
L4        1259 DUP REM L3 (628 DUPLICATES REMOVED)
L5           3 SEA L4 AND TOPICAL?
L6          30 SEA L5 OR L2


=> d ibib abs l6 1-30

L6  ANSWER 1 OF 30  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2002:794291  HCAPLUS
DOCUMENT NUMBER:         137:304819
TITLE:                   Regulation of epithelial tissue by hedgehog-like
                         polypeptides, and formulations and uses related
                         thereto
INVENTOR(S):             Wang, Elizabeth A.
PATENT ASSIGNEE(S):      USA
SOURCE:                  U.S. Pat. Appl. Publ., 72 pp., Cont.-in-part of U.S.
                         Ser. No. 955,552, abandoned.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  2
PATENT INFORMATION:

     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
     US 2002151460       A1   20021017      US 1998-151999   19980911
     CA 2307322          AA   19990429      CA 1998-2307322  19981020
     WO 9920298          A1   19990429      WO 1998-US22227  19981020
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9911089          A1   19990510      AU 1999-11089    19981020
     EP 1028741          A1   20000823      EP 1998-953814   19981020
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     JP 2001520202       T2   20011030      JP 2000-516694   19981020
PRIORITY APPLN. INFO.:                  US 1997-955552   B2 19971020
                                        US 1998-151999   A  19980911
                                        WO 1998-US22227  W  19981020
OTHER SOURCE(S):         MARPAT 137:304819
AB   The present application relates to a method for modulating the growth
     state of an epithelial cell by ectopically contacting the epithelial cell,
     in vitro or in vivo, with a hedgehog therapeutic or ptc therapeutic in an
     amt. effective to alter the rate (promote or inhibit) of proliferation of
     the epithelial cell, e.g., relative to the absence of administration of
     the hedgehog therapeutic or ptc (patched gene) therapeutic.  The subject
     method can be used, for example, to modulate the growth state of an
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epithelial tissue. such as for inducing the formation of skin or other cutaneous tissue, or for inducing growth of hair.

L6 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:272211 HCAPLUS
DOCUMENT NUMBER: 137:273131
TITLE: Sonic hedgehog
AUTHOR(S): Hattori, Hisashi; Mizutani, Hideki; Ueda, Minoru
CORPORATE SOURCE: Department of Oral and Maxillofacial Surgery, Nagoya University Graduate School of Medicine, Japan
SOURCE: Clinical Calcium (2002), 12(2), 233-237
CODEN: CLCCEJ; ISSN: 0917-5857
PUBLISHER: Iyaku Janarusha
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB We investigated ectopic cartilage and bone formation induced by transplantation of cells which were transfected with **Sonic hedgehog** (Shh) cDNA encoding amino-terminal **peptide** for gene therapy in bone regeneration. These results indicated Shh regulated early chondrogenesis and stimulation of prechondrocytes, and consequently the synergistic effects of Shh and BMP induced bone formation in vivo. In the future, further study of transfection of Shh combined with other gene groups regulating bone formation, or other bone-stimulating factors, or using new type of scaffold will be needed to confirm clin. application.

L6 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:695715 HCAPLUS
DOCUMENT NUMBER: 136:3216
TITLE: cGMP Enhances the Sonic Hedgehog Response in Neural Plate Cells
AUTHOR(S): Robertson, Christie P.; Gibbs, Sarah M.; Roelink, Henk
CORPORATE SOURCE: Department of Biological Structure, Program in Neurobiology and Behavior, and Center for Developmental Biology, University of Washington, Seattle, WA, 98195, USA
SOURCE: Developmental Biology (Orlando, FL, United States) (2001), 238(1), 157-167
CODEN: DEBIAO; ISSN: 0012-1606
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The elaboration of distinct cell types during development is dependent on a small no. of inductive mols. Among these inducers is Sonic hedgehog (Shh), which, in combination with other factors, patterns the dorsoventral (DV) axis of the nervous system. The response of a cell is dependent in part on its complement of cyclic nucleotides. CAMP antagonizes Shh signaling, and the authors examd. the influence of cGMP on the Shh response. Cells in chick neural plate explants respond to Shh by differentiating into ventral neural-cell types. Exposure of intermediate-zone explants to cGMP analogs enhanced their response to Shh in a dose-dependent manner. The Shh response was also enhanced in dorsal-zone explants exposed to chick natriuretic peptide (chNP), which stimulates cGMP prodn. by membrane-bound guanylate cyclase (mGC). Addn. of chNP to intermediate-zone explants did not enhance the Shh response, consistent with a reported lack of mGC in this region of the neural tube. Finally, the presence of a nitric oxide (NO)-sensitive guanylate cyclase (GC) was established by demonstrating cGMP immunoreactivity in neural

tissue following NO stimulation of whole chick embryos. Intracellular levels of cGMP and cAMP may thus provide a mechanism through which other factors modulate the Shh response during neural development. (c) 2001 Academic Press.

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:282104 HCAPLUS
DOCUMENT NUMBER: 135:222629
TITLE: The effects of 5-AZA-2'-deoxycytidine (d-AZA) on sonic hedgehog expression in mouse embryonic limb buds
AUTHOR(S): Branch, Stacy; Smoak, Ida W.
CORPORATE SOURCE: Department of Toxicology, North Carolina State University, Raleigh, NC, 27695, USA
SOURCE: Toxic Substance Mechanisms (2000), 19(2), 125-133
CODEN: TSUMEZ; ISSN: 1076-9188
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 5-Aza-2'-deoxycytidine (d-AZA) causes temporally-related defects in the mouse. At 1.0 mg/kg on gestational day (GD) 10, d-AZA causes hindlimb phocomelia. Sonic hedgehog (Shh) plays a significant role in the normal development of limbs in rodent species. **Sonic hedgehog peptides**, found in the posterior mesenchyme of limb buds, are involved in patterning functions and in the regulation of both anterior-posterior polarity and proximal-distal outgrowth of the limb. The objective of the present study was to analyze alterations in Shh expression subsequent to d-AZA exposure. Pregnant mice were treated with d-AZA via i.p. injection on GD 10. Controls were untreated. The reverse transcription-polymerase chain reaction (RT-PCR), whole mount in situ hybridization (ISH), and whole mount immunohistochem. (WMI) were used to analyze expression patterns of Shh. For FT-PCR, embryonic hindlimb buds (buds) were taken 0, 4, 8, 12, or 24 h after exposure. Cyclophilin was used as the baseline monitor. RNA was transcribed to cDNA and used as template with Shh specific primers for amplification. Whole embryos were collected 12 and 24 h posttreatment for ISH. An antisense primer specific for Shh was used in an oligo-based ISH protocol. Whole embryos were collected 36 and 48 h post-treatment for WMI. The antibody corresponding to the amino terminal subunit of the Shh peptide was used. There was a treatment related up-regulation of Shh transcripts by 12 and 24 h posttreatment. The protein response of up-regulation was detectable by 36 and 48 h posttreatment. Our data suggest that 5-aza-2'-deoxycytidine-induced hindlimb defects may be assocd. with alterations in the level of Shh expression. This may be part of a cascade of signaling events involved in d-AZA-induced hindlimb defects. Work is ongoing to det. the relationship of other gene species that may cooperate with Shh in the induction of the hindlimb defects.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137238 HCAPLUS
DOCUMENT NUMBER: 134:198026
TITLE: Peptides consisting of fragments of GLI-1 and SUFUH and their use
INVENTOR(S): Toftgard, Rune

PATENT ASSIGNEE(S): Karolinska Innovations AB, Swed.
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012655	A1	20010222	WO 2000-SE1576	20000814

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: SE 1999-2899 A 19990813

AB The present invention relates to the field of mammalian signalling pathways, and more precisely to the phys. interaction between two components of the Sonic hedgehog (Shh)-Patched (Ptch) signalling pathway, namely GLI-1 and SUFUH. The invention provides peptides consisting of fragments of GLI-1 and SUFUH, resp. which are able to specifically bind to SUFUH and GLI-1, resp. The invention also provides monoclonal antibodies and antibody fragments specifically binding to these peptides, as well as pharmaceutical compns. contg. the peptides, antibodies and/or antibody fragments, said pharmaceutical compns. being useful for treating cancer and diseases influencing cell differentiation and tissue development.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:901855 HCAPLUS
DOCUMENT NUMBER: 134:113556
TITLE: Sonic hedgehog regulates growth and morphogenesis of the tooth
AUTHOR(S): Dassule, Helene R.; Lewis, Paula; Bei, Marianna; Maas, Richard; McMahon, Andrew P.
CORPORATE SOURCE: Department of Molecular and Cellular Biology, The Biolabs, Cambridge, MA, 02138, USA
SOURCE: Development (Cambridge, United Kingdom) (2000), 127(22), 4775-4785
CODEN: DEVPED; ISSN: 0950-1991
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During mammalian tooth development, the oral ectoderm and mesenchyme coordinate their growth and differentiation to give rise to organs with precise shapes, sizes and functions. The initial ingrowth of the dental epithelium and its assocd. dental mesenchyme gives rise to the tooth bud. Next, the epithelial component folds to give the tooth its shape. Coincident with this process, adjacent epithelial and mesenchymal cells differentiate into enamel-secreting ameloblasts and dentin-secreting odontoblasts, resp. Growth, morphogenesis and differentiation of the

epithelium and mesenchyme are coordinated by secreted signaling proteins. **Sonic hedgehog** (Shh) encodes a signaling **peptide** which is present in the oral epithelium prior to invagination and in the tooth epithelium throughout its development. We have addressed the role of Shh in the developing tooth in mouse by using a conditional allele to remove Shh activity shortly after ingrowth of the dental epithelium. Redn. and then loss of Shh function results in a cap stage tooth rudiment in which the morphol. is severely disrupted. The overall size of the tooth is reduced and both the lingual epithelial invagination and the dental cord are absent. However, the enamel knot, a putative organizer of crown formation, is present and expresses Fgf4, Wnt10b, Bmp2 and Lef1, as in the wild type. At birth, the size and the shape of the teeth are severely affected and the polarity and organization of the ameloblast and odontoblast layers is disrupted. However, both dentin- and enamel-specific markers are expressed and a large amt. of tooth-specific extracellular matrix is produced. This observation was confirmed by grafting studies in which tooth rudiments were cultured for several days under kidney capsules. Under these conditions, both enamel and dentin were deposited even though the enamel and dentin layers remained disorganized. These studies demonstrate that Shh regulates growth and dets. the shape of the tooth. However, Shh signaling is not essential for differentiation of ameloblasts or odontoblasts.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:603796 HCAPLUS
DOCUMENT NUMBER: 133:278995
TITLE: Slow muscle induction by Hedgehog signalling in vitro
AUTHOR(S): Norris, Wendie; Neyt, Christine; Ingham, Phillip W.; Currie, Peter D.
CORPORATE SOURCE: Molecular Embryology Laboratory, Imperial Cancer Research Fund, London, WC2A 3PX, UK
SOURCE: Journal of Cell Science (2000), 113(15), 2695-2703
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Muscles are composed of several fiber types, the precise combination of which dets. muscle function. Whereas neonatal and adult fiber type is influenced by a no. of extrinsic factors, such as neural input and muscle load, there is little knowledge of how muscle cells are initially detd. in the early embryo. In the zebrafish, fibers of the slow twitch class arise from precociously specified myoblasts that lie close to the midline, whereas the remainder of the myotome differentiates as fast myosin expressing muscle. In vivo evidence has suggested the Sonic Hedgehog glycoprotein, secreted from the notochord, controls the formation of slow twitch and fast twitch muscle fates. Here the authors describe an in vitro culture system that they have developed to test directly the ability of zebrafish myoblasts to respond to exogenous **Sonic Hedgehog peptide**. The authors found that **Sonic Hedgehog peptide** can control the binary cell fate choice of embryonic zebrafish myoblasts in vitro. The authors have also used this culture system to assay the relative activities of different Hedgehog-family proteins and to investigate the possible involvement of heterotrimeric G-proteins in Hedgehog signal transduction.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:446518 HCAPLUS
DOCUMENT NUMBER: 133:175046
TITLE: The bHlH transcription factor dHAND controls Sonic hedgehog expression and establishment of the zone of polarizing activity during limb development
AUTHOR(S): Charite, Jeroen; McFadden, David G.; Olson, Eric N.
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75390-9148, USA
SOURCE: Development (Cambridge, United Kingdom) (2000), 127(11), 2461-2470
CODEN: DEVPED; ISSN: 0950-1991
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Limb outgrowth and patterning of skeletal elements are dependent on complex tissue interactions involving the zone of polarizing activity (ZPA) in the posterior region of the limb bud and the apical ectodermal ridge. The **peptide** morphogen **Sonic hedgehog** (SHH) is expressed specifically in the ZPA and, when expressed ectopically, is sufficient to mimic its functions, inducing tissue growth and formation of posterior skeletal elements. We show that the basic helix-loop-helix transcription factor dHAND is expressed posteriorly in the developing limb prior to Shh and subsequently occupies a broad domain that encompasses the Shh expression domain. In mouse embryos homozygous for a dHAND null allele, limb buds are severely underdeveloped and Shh is not expressed. Conversely, misexpression of dHAND in the anterior region of the limb bud of transgenic mice results in formation of an addnl. ZPA, revealed by ectopic expression of Shh and its target genes, and resulting limb abnormalities that include preaxial polydactyly with duplication of posterior skeletal elements. Anal. of mouse mutants in which Hedgehog expression is altered also revealed a feedback mechanism in which Hedgehog signaling is required to maintain the full dHAND expression domain in the developing limb. Together, these findings identify dHAND as an upstream activator of Shh expression and important transcriptional regulator of limb development.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:421167 HCAPLUS
DOCUMENT NUMBER: 133:68974
TITLE: Methods and compositions using hedgehog polypeptides for treating disorders involving excitotoxicity
INVENTOR(S): Galdes, Alphonse; Mahanthappa, Nagesh
PATENT ASSIGNEE(S): Biogen, Inc., USA; Ontogeny, Inc.
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000035948	A1	20000622	WO 1999-US28721	19991203
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 9928343	A2	19990610	WO 1998-US25676	19981203
WO 9928343	A3	19990812		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1135411	A1	20010926	EP 1999-967188	19991203
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:	WO 1998-US25676	W	19981203
	US 1999-238243	A	19990127
	US 1999-325602	A	19990603
	US 1997-67423P	P	19971203
	US 1998-78935P	P	19980320
	US 1998-89685P	P	19980617
	US 1998-99800P	P	19980910
	WO 1999-US28721	W	19991203

AB It is shown here that hedgehog polypeptides possess activities beyond phenotype specification. Using cultures derived from the embryonic day 14.5 (E14.5) rat ventral mesencephalon, we show that hedgehog is also trophic for dopaminergic neurons and other neurons which are sensitive to excitotoxicity.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 30 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2000:288262 HCAPLUS
DOCUMENT NUMBER:	133:206289
TITLE:	**Sonic hedgehog** signal **peptide** mutation in a patient with holoprosencephaly
AUTHOR(S):	Kato, Mitsuhiro; Nanba, Eiji; Akaboshi, Shinjiro; Shiihara, Takashi; Ito, Aiko; Honma, Tomomi; Tsuburaya, Kenji; Hayasaka, Kiyoshi
CORPORATE SOURCE:	Department of Pediatrics, Yamagata University School of Medicine, Yamagata, 990-9585, Japan
SOURCE:	Annals of Neurology (2000), 47(4), 514-516 CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB The authors investigated the mol. basis of holoprosencephaly in a sporadic

patient and identified a novel missense mutation in the signal sequence of the sonic hedgehog (Shh) gene. Magnetic resonance imaging of the head showed a lobar type of holoprosencephaly and partial agenesis of the anterior corpus callosum. He was treated for craniosynostosis at 7 mo of age. All three exons of the Shh gene were amplified by polymerase chain reaction from genomic DNA of the patient and controls. Sequencing anal. of the polymerase chain reaction fragments, screened by single-strand conformation polymorphism anal., revealed a heterozygous mutation of a T-to-C substitution at nucleotide position 50. This mutation predicted an amino acid replacement of leucine to proline at codon 17 located in the signal peptide of SHH protein. It probably disturbs the translocation of the protein into the endoplasmic reticulum and may lead to holoprosencephaly because of haploinsufficiency of Shh.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:227528 HCAPLUS
DOCUMENT NUMBER: 132:270066
TITLE: Hedgehog and patched antagonists for inhibiting cell and tissue growth and differentiation and uses thereof
INVENTOR(S): Burkly, Linda; Wang, Li Chun
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018428	A2	20000406	WO 1999-US20852	19990910
WO 2000018428	A3	20000525		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2343335	AA	20000406	CA 1999-2343335	19990910
AU 9959186	A1	20000417	AU 1999-59186	19990910
EP 1112087	A2	20010704	EP 1999-946873	19990910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2002015702	A1	20020207	US 2001-804490	20010312

PRIORITY APPLN. INFO.: US 1998-100037P P 19980911
WO 1999-US20852 W 19990910

AB A method for inhibiting growth or differentiation of an epithelial cell comprising contacting at least an epithelial cell with an effective amt. of an agent selected from the group consisting of a hedgehog antagonist and a patched antagonist.

L6 ANSWER 12 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:746003 HCAPLUS

DOCUMENT NUMBER: 132:120102
TITLE: Sonic hedgehog signaling during digit pattern duplication after application of recombinant protein and expressing cells
AUTHOR(S): Wada, Naoyuki; Kawakami, Yasuhiko; Nohno, Tsutomu
CORPORATE SOURCE: Department of Molecular Biology, Kawasaki Medical School, Kurashiki, 701-0192, Japan
SOURCE: Development, Growth & Differentiation (1999), 41(5), 567-574
CODEN: DGDFA5; ISSN: 0012-1592
PUBLISHER: Blackwell Science Asia Pty Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HoxD expression and cartilage pattern formation were compared after application of a recombinant N-terminal **peptide** of **Sonic hedgehog** protein (Shh-N) and implantation of cells expressing the Sonic hedgehog (Shh) gene. During digit duplication after implantation of a Shh-N-soaked bead, BMP-2 and Patched expression was transiently induced in the anterior limb mesenchyme 20 h after grafting, but was reduced to the basal level 48 h after grafting. On the contrary, when Shh-expressing cells were grafted to the anterior limb bud, expression domains of the BMP-2 and Patched genes were initially induced in the restricted region in close proximity to the grafted cells. Induced expression of BMP-2 and Patched was maintained in the anterior-peripheral region of the limb bud for 42 h after grafting. In either case, HoxD12 and HoxD13 were consistently induced in the anterior-distal limb mesenchyme, accompanying mirror-image duplication of the digit pattern. Induction and maintenance of HoxD expression were consistent with the resultant digit pattern. A steep gradient of Shh activity provided by Shh-expressing cells is most adequate to induce complete digit pattern, as compared to the shallow gradient provided by Shh-N protein released from a bead. These results suggest that positional identity is respecified by Shh-N activity within the first 24 h during digit duplication, and that Shh-N on its own is not acting as a long-range signaling mol. to det. positional identity at a distance in the limb bud.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:282115 HCAPLUS
DOCUMENT NUMBER: 130:320865
TITLE: Regulation of epithelial tissue by hedgehog-like polypeptides for stimulation of skin or hair formation
INVENTOR(S): Wang, Elizabeth A.
PATENT ASSIGNEE(S): Ontogeny, Inc., USA
SOURCE: PCT Int. Appl., 146 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920298	A1	19990429	WO 1998-US22227	19981020

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,

KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002151460	A1	20021017	US 1998-151999	19980911
CA 2307322	AA	19990429	CA 1998-2307322	19981020
AU 9911089	A1	19990510	AU 1999-11089	19981020
EP 1028741	A1	20000823	EP 1998-953814	19981020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001520202	T2	20011030	JP 2000-516694	19981020

PRIORITY APPLN. INFO.:
US 1997-955552 A 19971020
US 1998-151999 A 19980911
WO 1998-US22227 W 19981020

OTHER SOURCE(S): MARPAT 130:320865

AB The present application relates to a method for modulating the growth state of an epithelial cell by ectopically contacting the epithelial cell, in vitro or in vivo, with a hedgehog therapeutic or ptc therapeutic in an amt. effective to alter the rate (promote or inhibit) of proliferation of the epithelial cell, e.g., relative to the absence of administration of the hedgehog therapeutic or ptc (patched gene) therapeutic. The subject method can be used, for example, to modulate the growth state of an epithelial tissue, such as for inducing the formation of skin or other cutaneous tissue, or for inducing growth of hair.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:765995 HCAPLUS
DOCUMENT NUMBER: 130:180417
TITLE: Regulation of chondrogenesis in the developing inner ear: a role for sonic hedgehog
AUTHOR(S): Frenz, D. A.; Doan, T. M.; Liu, W.
CORPORATE SOURCE: Department of Otolaryngology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Annals of the New York Academy of Sciences (1998), 857(Morphogenesis: Cellular Interactions), 252-255
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Sonic hedgehog** (Shh) **peptide** alone did not initiate chondrogenesis in cultured periotic mesenchyme, but enhanced the chondrogenic differentiation. Suppression of chondrogenesis by Shh antisense oligonucleotide suggests participation of Shh at the onset of epithelial-mesenchymal interactions in the developing inner ear.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:481826 HCAPLUS
DOCUMENT NUMBER: 127:157237
TITLE: Molecular mechanisms of tooth development
AUTHOR(S): Noji, Sumihare
CORPORATE SOURCE: Department Biological Science Technology, Faculty

Engineering, University Tokushima, Tokushima City, 770, Japan
SOURCE: Shika Kiso Igakkai Zasshi (1997), 39(3), 189-201
CODEN: SHKKAN; ISSN: 0385-0137
PUBLISHER: Shika Kiso Igakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB Recent progress in elucidation of mechanisms of tooth development was reviewed with 33 refs. Many genes expressed during tooth development have been identified. For example, homeobox genes such as Msx, Dlx, Barx and **peptide** growth factors such as **Sonic hedgehog** (SHH), BMP, FGF, HGF, etc. are expressed in tooth buds and probably play important roles for tooth morphogenesis. Since Msx, Dlx, and Barx are expressed differentially during tooth formation, combination of expression patterns of these genes may be related to dentition and tooth morphol. On the other hand, differentiation of the tooth bud may be regulated by epithelial-mesenchymal interaction which is mediated by SHH, BMP4, BMP2, FGF4, and Notchs. These genes are also expressed during development of various organs other than tooth. They are vertebrate homologues of Drosophila genes which functions during insect morphogenesis. Thus, it seems likely that fundamental mechanisms underlying tooth development are common over other organs such as limbs, guts and lungs in vertebrates as well as in insects.

L6 ANSWER 16 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:219429 HCAPLUS
DOCUMENT NUMBER: 126:304073
TITLE: Post-translational processing and renal expression of mouse Indian hedgehog
AUTHOR(S): Valentini, Rudolph P.; Brookhiser, William T.; Park, John; Yang, Tianxin; Briggs, Josephine; Dressler, Gregory; Holzman, Lawrence B.
CORPORATE SOURCE: Medical School, University of Michigan, Ann Arbor, MI, 48109-0676, USA
SOURCE: Journal of Biological Chemistry (1997), 272(13), 8466-8473
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The full-length mouse Indian hedgehog (Ihh) cDNA was cloned from an embryonic 17.5-day kidney library and was used to study the post-translational processing of the peptide and temporal and spatial expression of the transcript. Sequence anal. predicted two putative translation initiation sites. Ihh translation was initiated at both initiation sites when expressed in an in vitro transcription/translation system. Expression of an Ihh mutant demonstrated that the internal translation initiation site was sufficient to produce the mature forms of Ihh. Ihh post-translational processing proceeded in a fashion similar to **Sonic** and Drosophila **hedgehog**: the unprocessed form underwent signal **peptide** cleavage as well as internal proteolytic processing to form a 18-kDa amino-terminal peptide and a 26-kDa carboxyl-terminal peptide. This processing required His313 present in a conserved serine protease motif. Ihh transcript was detected by in situ RNA hybridizations as early as 10 days postcoitum (dpc) in developing gut, as early as 14.5 dpc in the cartilage primordium, and in the

developing urogenital sinus. In semiquant. reverse transcription-polymerase chain reaction expts., Indian hedgehog transcript was first detected in the mouse metanephros at 14.5 dpc; transcript abundance increased with gestational age, becoming maximal in adulthood. In adult kidney, Ihh transcript was detected only in the proximal convoluted tubule and proximal straight tubule.

L6 ANSWER 17 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:98845 HCAPLUS
DOCUMENT NUMBER: 124:138757
TITLE: Sonic hedgehog: making the gradient
AUTHOR(S): Bumcrot, David A.; McMahon, Andrew P.
CORPORATE SOURCE: Dep. Mol. Cell. Biol., Harvard Univ., Cambridge, MA, 02138, USA
SOURCE: Chemistry & Biology (1996), 3(1), 13-16
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Current Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 23 refs. The amino-terminal **peptide** of **Sonic hedgehog** is a cell-tethered mol., which nevertheless seems to provide a developmental signal that acts at a distance and has different effects depending on its concn. Recent structural data suggest that zinc-dependent proteolysis may somehow be involved in sonic hedgehog's function.

L6 ANSWER 18 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:912220 HCAPLUS
DOCUMENT NUMBER: 123:310774
TITLE: Induction of dopaminergic neuron phenotype in the midbrain by Sonic hedgehog protein
AUTHOR(S): Wang, Monica Z.; Jin, Ping; Bumcrot, David A.; Marigo, Valaria; McMahon. Andrew P.; Wang, Elizabeth A.; Woolf, Tod; Pang, Kevin
CORPORATE SOURCE: Ontogeny, Inc., Cambridge, MA, 02139, USA
SOURCE: Nature Medicine (New York) (1995), 1(11), 1184-8
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature Publishing Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Loss of substantia nigra dopaminergic neurons, which develop from the ventral region of the midbrain, is assocd. with Parkinson's disease. During embryogenesis, induction of these and other ventral neurons is influenced by interactions with the underlying mesoderm of the notochord and the floor plate, which lies at the ventral midline of the developing CNS. **Sonic hedgehog** encodes a secreted **peptide**, which is expressed in notochord and floor plate cells and can induce appropriate ventral cell types in the basal forebrain and spinal cord. Here the authors demonstrate that Sonic hedgehog is sufficient to induce dopaminergic and other neuronal phenotypes in chick mesencephalic explants in vitro. The authors find that Sonic hedgehog is a general ventralizing signal in the CNS, the specific response being detd. by the receiving cells. These results suggest that Sonic hedgehog may have utility in the induction of clin. important cell types.

L6 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:750315 HCAPLUS

TITLE: Distribution of **Sonic hedgehog peptides** in the developing chick and mouse embryo
AUTHOR(S): Marti, Elisa; Takada, Ritsuko; Bumcrot, David A.; Sasaki, Hiroshi; McMahon, Andrew P.
CORPORATE SOURCE: Dept. Mol. and Cellular Biol., Harvard Univ., Cambridge, MA, 02138, USA
SOURCE: Development (Cambridge, United Kingdom) (1995), 121(8), 2537-47
CODEN: DEVPED; ISSN: 0950-1991
PUBLISHER: Company of Biologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sonic hedgehog (Shh) encodes a signal that is implicated in both short- and long-range interactions that pattern the vertebrate central nervous system (CNS), somite and limb. Studies in vitro indicate that Shh protein undergoes an internal cleavage to generate two secreted peptides. We have investigated the distribution of Shh peptides with respect to these patterning events using peptide-specific antibodies. Immunostaining of chick and mouse embryos indicates that Shh peptides are expressed in the notochord, floor plate and posterior mesenchyme of the limb at the appropriate tims for their postulated patterning functions. The amino peptide that is implicated in intercellular signaling is secreted but remains tightly assocd. with expressing cells. The distribution of peptides in the ventral CNS is polarized with the highest levels of protein accumulating towards the luminal surface. Interestingly, Shh expression extends beyond the floor plate, into ventro-lateral regions from which some motor neuron precursors are emerging. In the limb bud, peptides are restricted to a small region of posterior-distal mesenchyme in close assocn. with the apical ectodermal ridge; a region that extends 50-75 .mu.m along the anterior-posterior axis. Temporal expression of Shh peptides is consistent with induction of sclerotome in somites and floor plate and motor neurons in the CNS, as well as the regulation of anterior-posterior polarity in the limb. However, we can find no direct evidence for long-range diffusio nof the 19.times.103 Mr peptide which is thought to mediate both short- and long-range cell interactions. Thus, either long-range signaling is mediated indirectly by the activation of other signals, or alternatively the low levels of diffusing peptide are undetectable using available techniques.

L6 ANSWER 20 OF 30 MEDLINE
ACCESSION NUMBER: 2002658327 MEDLINE
DOCUMENT NUMBER: 22305193 PubMed ID: 12417650
TITLE: Pituitary adenylate cyclase-activating **polypeptide** and **sonic hedgehog** interact to control cerebellar granule precursor cell proliferation.
AUTHOR: Nicot Arnaud; Lelievre Vincent; Tam Jimmy; Waschek James A; DiCicco-Bloom Emanuel
CORPORATE SOURCE: Department of Neuroscience and Cell Biology, University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School, Piscataway, New Jersey 08854, USA.. nicotar@umdnj.edu
CONTRACT NUMBER: HD0461 (NICHD)
HD06576 (NICHD)
HD34475 (NICHD)
NS 32401 (NINDS)
SOURCE: JOURNAL OF NEUROSCIENCE, (2002 Nov 1) 22 (21) 9244-54.

Journal code: 8102140. ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021107
Last Updated on STN: 20021212
Entered Medline: 20021125

AB Although positive and negative signals control neurogenesis in the embryo, factors regulating postnatal proliferation are less well characterized. In the vertebrate cerebellum, Sonic Hedgehog (Shh) is an efficacious mitogen for cerebellar granule neuron precursors (GNPs), and mutations activating the Shh pathway are linked to medulloblastoma, a tumor derived from GNPs. Although the mitogenic effects of Shh can be blocked by increasing cAMP or protein kinase A activity, the physiological factors antagonizing this stimulation are undefined. In the embryo, pituitary adenylate cyclase-activating polypeptide (PACAP) receptor 1 (PAC1) signaling regulates neural precursor proliferation. We now show that in the developing cerebellum, PAC1 mRNA colocalizes with gene transcripts for Shh receptor Patched 1 and target gene Gli1 in the external germinal layer. We consequently investigated the interactions of PACAP and Shh in proliferation of purified GNPs in culture. Shh exhibited mitogenic activity in both rat and mouse cultures, stimulating DNA synthesis approximately 10-fold after 48 hr of exposure. PACAP markedly inhibited Shh-induced thymidine incorporation by 50 and 85% in rat and mouse GNPs, respectively, but did not significantly affect the stimulation induced by other mitogens. This selective effect was reproduced by the specific PAC1 agonist maxadilan, as well as by the adenylate cyclase activator forskolin, suggesting that PAC1 provides a potent inhibitory signal for Shh-induced proliferation in developing cerebellum. In contrast, in the absence of Shh, PACAP and maxadilan modestly stimulated DNA synthesis, an effect reproduced by activating protein kinase C. These observations suggest that G-protein-coupled receptors, such as PAC1, serve as sensors of environmental cues, coordinating diverse neurogenetic signals.

L6 ANSWER 21 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002362371 EMBASE
TITLE: The human prostate expresses Sonic hedgehog during fetal development.
AUTHOR: Barnett D.H.; Huang H.-Y.; Wu X.-R.; Laciak R.; Shapiro E.; Bushman W.
CORPORATE SOURCE: W. Bushman, Division of Urology, Department of Surgery, Univ. of Wisconsin Medical School, Madison, WI, United States
SOURCE: Journal of Urology, (1 Nov 2002) 168/5 (2206-2210).
Refs: 20
ISSN: 0022-5347 CODEN: JOURAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
021 Developmental Biology and Teratology
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose: The keynote event of prostate ductal development is the formation

of epithelial buds that invade the urogenital sinus mesenchyma. Studies in mice have shown that budding requires the signaling **peptide Sonic hedgehog**, which is expressed in the epithelium of the prostatic anlagen. We report our characterization of sonic hedgehog (SHH) expression in the human fetal prostate. Materials and Methods: Reverse transcriptase-polymerase chain reaction was performed in fetal prostate RNA isolated at 15.5 and 18 weeks of gestation, respectively. Immunostaining was performed on sections from 7 male fetuses at 9.5 to 34 and in 4 female fetuses at 9 to 18 weeks of gestation. Results: Weak staining for SHH was seen in the prostatic urethra at 9.5 weeks. Intense staining was seen at 11.5 and 13 weeks in the prostatic urothelium and nascent prostatic buds. Staining was slightly diminished at 16.5, further diminished at 18 to 20 and absent at 34 weeks. SHH expression at 15.5 and 18 weeks was confirmed by reverse transcriptase-polymerase chain reaction assay of freshly isolated prostate tissue. Comparative SHH immunostaining in the female showed urothelial staining at 9 and 12 weeks with staining greatest above the entrance of the mullerian ducts. Staining diminished earlier in the female (14 weeks) than in the male and was almost absent at 18 weeks. Conclusions: SHH expression in the human fetal prostate is contemporaneous with the fetal testosterone surge and with ductal budding of the prostatic urothelium. SHH expression is also present in the female urogenital sinus but in the absence of testosterone it is not associated with ductal budding.

L6 ANSWER 22 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:2678 BIOSIS
DOCUMENT NUMBER: PREV200200002678
TITLE: Anterograde axonal transport of **Sonic Hedgehog peptides** in the hamster retinal projection.
AUTHOR(S): Faure, H. (1); Moya, K. L.; Hassig, R.; Ruat, M. (1); Traiffort, E. (1)
CORPORATE SOURCE: (1) UPR9040-CNRS, Gif-sur-Yvette France
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2123. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB In addition to their expression during embryogenesis, Sonic Hedgehog (Shh) mRNAs are transcribed in the adult brain and in the spinal cord suggesting additional roles for this morphogen in adult neural tissues (Traiffort et al, 1999). Using 167Ab rabbit antibodies recognizing the aminoterminal fragment of Shh (ShhN), we have identified a 22 kDa ShhN immunoreactive peptide in several hamster brain areas where Shh transcripts have not been previously detected such as the hippocampus and the superior colliculus (SC) suggesting that neuronal Shh is synthesized at a distance and conveyed in projecting axons. In order to examine this possibility, we analyzed Shh expression and transport in the primary hamster visual system. In the adult primary visual pathway, ShhN was most abundant in the SC, less in the optic nerve and low in the retina. Analysis of 2-D blots containing metabolically labeled retinal ganglion cell proteins transported to the SC with 167Ab, showed that hamster ShhN in the SC migrated as a single, tightly focussed protein. Alignment of the ECL films and autoradiograms showed that the ShhN spot overlaps perfectly with a

radiolabeled protein 48 hours after intraocular injection consistent with the synthesis of ShhN in retinal ganglion cells and its axonal transport to the SC. Analysis of this axonal transport profile differs from that of transmembrane proteins destined for the axon terminal. Our data suggest that Shh protein could act at a distance from its site of synthesis after axonal transport, and raise the possibility for additional roles for Shh in the mature visual system and in the adult brain.

L6 ANSWER 23 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:430035 BIOSIS
DOCUMENT NUMBER: PREV200100430035
TITLE: The whereabouts of a morphogen: Direct evidence for short- and graded long-range activity of Hedgehog signaling peptides.
AUTHOR(S): Gritli-Linde, Amel (1); Lewis, Paula; McMahon, Andrew P.; Linde, Anders
CORPORATE SOURCE: (1) Department of Oral Biochemistry, Goteborg University, SE-405 30, Goteborg: amel@odontologi.gu.se Sweden
SOURCE: Developmental Biology, (August 15, 2001) Vol. 236, No. 2, pp. 364-386. print.
ISSN: 0012-1606.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Sonic Hedgehog (Shh) and Indian Hedgehog (Ihh) are members of the Hedgehog (Hh) family of signaling molecules known to be involved in embryonic patterning and morphogenesis. The Hh proteins undergo an autocatalytic cleavage to yield an N-terminal and a C-terminal peptide, with the signaling capacities confined to the N peptide. Drosophila Hh-N has been shown to act via both short- and long-range signaling. In vertebrates, however, attempts to directly demonstrate Shh (SHH) or Ihh (IHH) proteins at a distance from producing cells have been largely unsuccessful. Furthermore, the fact that the Hh N peptides occur in a cholesterol-modified, membrane-tethered form is not easily reconciled with long-range signaling. This study used optimized immunohistochemistry combined with tissue separation and biochemical analyses in vivo and in vitro to determine the range of action of SHH and IHH in the mouse embryo. In all embryonic structures studied, we detect signaling peptides in producing cells, but we also find that ligands move over considerable distances depending on the tissue. These data provide direct evidence for the presence of Hedgehog signaling peptides in target compartments, suggesting a direct long-range action without a need for secondary mediators. Visualization of Hedgehog proteins in target tissues was achieved only under conditions that allowed proteoglycan/glycosaminoglycan (PG/GAG) preservation. Furthermore, we show that induced changes of the composition of PG/GAG in the tooth alter SHH signaling. These data suggest a crucial role for PG/GAGs in Hedgehog movement.

L6 ANSWER 24 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:82855 BIOSIS
DOCUMENT NUMBER: PREV200100082855
TITLE: The sonic hedgehog pathway is present in human T lymphocytes.
AUTHOR(S): Stewart, G. A. (1); Lindey, S. (1); Lamb, J. R. (1); Howie, S. E. M. (1); Hoyne, G. F. (1)
CORPORATE SOURCE: (1) Immunobiology Group, MRC Centre for Inflammation Research, Edinburgh University Medical School, Teviot

Place, Edinburgh, EH8 9AG UK
SOURCE: Immunology, (December, 2000) Vol. 101, No. Supplement 1, pp. 14. print.
Meeting Info.: Annual Congress of the British Society for Immunology Harrogate, UK December 05-08, 2000 British Society for Immunology
. ISSN: 0019-2805.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L6 ANSWER 25 OF 30 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-34572 DRUGU P B
TITLE: Effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine.
AUTHOR: Taipale J; Chen J K; Cooper M K; Wang B; Mann R K; Milenkovic L; Scott M P; Beachy P A
CORPORATE SOURCE: Univ.Johns-Hopkins; Univ.Stanford
LOCATION: Baltimore, Md.; Stanford, Cal., USA
SOURCE: Nature (406, No. 6799, 1005-09, 2000) 4 Fig. 1 Tab. 29 Ref.
CODEN: NATUAS ISSN: 0028-0836
AVAIL. OF DOC.: Department of Molecular Biology and Genetics, Howard Hughes Medical Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, U.S.A. (P.A.B.).
(e-mail: pbeachy@jhmi.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2000-34572 DRUGU P B
AB The mechanisms of action involved in the cytostatic activity of cyclopamine were investigated in-vitro. Cyclopamine, and its derivative, 3-keto,N-aminomethyl aminocaproyl dihydrocinamoyl cyclopamine (KAAD-cyclopamine), blocked the activation of the Hedgehog (Hh) response pathway and abnormal cell growth associated with oncogenic mutations that activate the proto-oncogene Smoothened (Smo) or that inactivate the tumor suppresser Patched (Ptch). Cyclopamine may act by influencing the balance between active and inactive forms of Smo.
ABEX Treatment of NIH-3T3 mouse embryonic fibroblasts, which responded to palmitoyl and cholesteryl-modified **Sonic hedgehog** N **polypeptide** (ShhNp) with a 20-150-fold induction of luciferase activity, with cyclopamine completely abolished the response to ShhNp. Addition of cyclopamine to fibroblasts derived from Ptch-/- mouse embryos suppressed beta-galactosidase expression (which is under the control of the Ptch promoter) and the activity of the Gli-luc reporter. NIH-3T3 cells were transiently transfected with both luciferase reporter and Smo complementary DNA, and overexpression of Smo in the absence of Shh induced reporter expression about 10-fold. This Shh-independent activation of the response pathway was suppressed by cyclopamine (5 uM). The cyclopamine derivative KAAD-cyclopamine had 10-20-fold higher potency that cyclopamine in inhibition of beta-galactosidase expression in Ptch-/- cells, with similar or lower toxicity. This compound also had greater potency in suppression of ShhNp-induced pathway activity. Ptch-/- cell growth in low serum was markedly inhibited by addition of KAAD-cyclopamine, with an IC50 of 50 nM. KAAD-cyclopamine also inhibited the growth of SmoA1-LIGHT cells, which express SmoA1 clonally derived from NIH-3T3 cells, with an IC50 of about 500 nM. (SK)

L6 ANSWER 26 OF 30 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-20029 DRUGU P
TITLE: Therapeutic potential of nerve growth factors in Parkinson's disease.
AUTHOR: Collier T J; Sortwell C E
LOCATION: Chicago, Ill., USA
SOURCE: Drugs Aging (14, No. 4, 261-87, 1999) 3 Tab. 215 Ref.
CODEN: DRAGE ISSN: 1170-229X
AVAIL. OF DOC.: Department of Neurological Sciences, Center for Brain Repair, Rush-Presbyterian St. Luke's Medical Center, 2242 West Harrison Street, Suite 200, Chicago, IL 60612, U.S.A. (e-mail: tcollier@rush.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1999-20029 DRUGU P
AB The treatment of Parkinson's disease with nerve growth factors (fibroblast growth factor, epidermal growth factor, transforming growth factor-alpha, platelet-derived growth factor, transforming growth factor-beta, glial cell line-derived neurotrophic factor and neurotrophins (3, 4/5 and 6) and brain-derived neurotrophic factor, interleukins 1-12, ciliary neuronotrophic factor, monosialoganglioside, **peptide** encoding the **Sonic hedgehog** gene and immunophilin ligands (ciclosporin and tacrolimus)) is reviewed with reference to bioassays, neurotrophic factors for dopaminergic neurons, biological rationale for growth factor therapy and problems and challenges in treatment. Neurotrophic strategies warrant development for treatment of Parkinson's disease with further investigation for specific, potent and long-lasting agents and methods of drug-targeting.
ABEX At present only the symptoms of Parkinson's disease can be treated as the disease progresses and drugs lose their efficacy. The use of neurotrophic factors may be useful to stabilize the diminishing population of dopaminergic neurones, stimulating compensation and growth in the cells. 29 Different molecules with neurotrophic properties for dopaminergic neurons are discussed. The timing of intervention to examine neuroregeneration is very important. Cell cultures and animal models are examined with the various agents and the data discussed with relevance to treatment of Parkinson's disease. (E93)

L6 ANSWER 27 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-049316 [06] WPIX
DOC. NO. NON-CPI: N2002-036468
DOC. NO. CPI: C2002-013864
TITLE: Using Sonic and Indian hedgehog proteins as trophic factors to stimulate production of cartilage by chondrocytes, e.g. for the replacement of damaged tissue.
DERWENT CLASS: A96 B04 D15 D22 P34
INVENTOR(S): BLUNK, T; GOEPFERICH, A; KELLNER, K; LANG, K; LESER-REIFF, U; PAPADIMITRIOU, A; SCHULTZ, M
PATENT ASSIGNEE(S): (BLUN-I) BLUNK T; (GOEP-I) GOEPFERICH A; (KELL-I) KELLNER K; (LANG-I) LANG K; (LESE-I) LESER-REIFF U; (PAPA-I) PAPADIMITRIOU A; (SCHU-I) SCHULTZ M; (CURI-N) CURIS INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001082994	A1	20011108	(200206)*	EN	18

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

US 2002015719 A1 20020207 (200213)

AU 2001055767 A 20011112 (200222)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001082994	A1	WO 2001-US13819	20010427
US 2002015719	A1 Provisional	US 2000-200767P	20000428
		US 2001-844257	20010427
AU 2001055767	A	AU 2001-55767	20010427

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001055767	A Based on	WO 200182994

PRIORITY APPLN. INFO: US 2000-200767P 20000428; US 2001-844257 20010427

AN 2002-049316 [06] WPIX

AB WO 200182994 A UPAB: 20020128

NOVELTY - The use of sonic and Indian hedgehogs to modulate the growth of and/or cartilage production by chondrocytes, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (I) of making a cartilaginous prosthesis, comprising seeding a polymeric matrix construct with chondrocytes and contacting the seeded construct with a hedgehog therapeutic; and

(2) a tissue culture system (II) for the production of cartilage comprising a polymeric matrix, chondrocytes adherent to the matrix and a culture medium comprising a hedgehog therapeutic that causes a increase in the proteoglycan content of the cartilage (compared to the content in the absence of the hedgehog therapeutic).

ACTIVITY - Antitraumatic.

Bovine articular chondrocytes were isolated from the femoropatellar groove of 6 week-old calves. Cells were isolated and cultivated as previously described. The chondrocytes were cultured on PGA (polyglycolid acid) scaffolds. The scaffolds were produced by extruding PGA into 13 micrometer-diameter fibbers and processing these into fibrous discs measuring 5 mm in diameter and 2 mm in thickness (bulk density of 43 mg/cm cubed). As sonic hedgehog (shh) is found to be tethered to cell membranes for example in a form that contains a palmitoyl group, dipalmitylated sonic hedgehog (dp-shh), dipalmitylated Indian hedgehog (dp-ihh) and sonic hedgehog dimer (shh-dimer) were used in varying concentrations supplemented to the culture medium. Isolated chondrocytes were seeded onto the scaffolds in a spinner-flask for 2 days at 80 rpm in an incubator at 37 degrees Centigrade, 5% CO2 and 95 % humidity. Each

scaffold was then placed in a 6-well plate in 6 ml culture medium containing 1 % FBS and put on an orbital shaker at 50 rpm. After two days the culture medium was changed and from this time point the effector molecules were added in varying concentrations with each medium change. Medium was replaced 3 times per week for up to 4 weeks. Directly after harvesting the constructs were weighed (=wet weight) and cut in halves. One part was prepared as histological sample (safranin-O staining for proteoglycan and immunohistological collagen type II staining), the other part was used for biochemical analysis. Therefore this part was freeze-dried, digested overnight with papainase and then analyzed for cell number, content of total collagen and proteoglycan content of the cell-polymer construct. After four weeks a dose-dependent increase in wet weight, tissue size and mechanical resistance, tissue size and mechanical resistance was detected for all cell-polymer constructs receiving hedgehog proteins, with dipalmitoyl-sonic hedgehog at c = 1000 ng/ml showing the largest response. Collagen amount generally increased proportionally with increasing construct weight. Collagen type tI as marker for differentiated chondrocytes was detected in abundance in all samples. A great concentration-dependent influence on proteoglycan content was determined for all hedgehog proteins. Proteoglycan content increased to an even larger extent than the wet weight of the constructs, therefore leading to an improved biochemical composition of the tissue. Dipalmitoyl-sonic hedgehog showed the largest effects of all at c = 1000 ng/ml (2.7 fold increase compared to control constructs receiving no exogenous hedgehog protein). Additionally the cell number per wet weight decreased with increasing hedgehog concentrations. Taken together with the increased cumulated amounts of proteoglycan and collagen the data suggested an increased ECM production for each cell. In general hedgehog proteins led to a higher proteoglycan content, a more equivalent distribution of proteoglycan and in addition a more mature tissue with bigger and a lower number of cells in the cell-polymer construct.

MECHANISM OF ACTION - Protein therapy (the hedgehogs act as trophic factors).

USE - The hedgehogs are used to modulate the growth of and/or production of cartilage by chondrocytes (i.e. is acts as a trophic factor) especially for developing cartilaginous tissue ex vivo suitable for implantation to replace damaged or deteriorated cartilage in a patient.

Dwg.0/3

L6 ANSWER 28 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-540411 [60] WPIX
DOC. NO. CPI: C2001-161271
TITLE: Forming dopaminergic neurons for treating disorders due to abnormalities in postural reflux regulation, involves contacting neuroprogenitor cells with fibroblast growth factor-8 and **sonic hedgehog polypeptide.**
DERWENT CLASS: B04 D16
INVENTOR(S): HYNES, M A; ROSENTHAL, A; YE, W
PATENT ASSIGNEE(S): (GETH) GENENTECH INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6277820	B1	20010821	(200160)*		48

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6277820	B1	US 1998-57860	19980409

PRIORITY APPLN. INFO: US 1998-57860 19980409
AN 2001-540411 [60] WPIX
AB US 6277820 B UPAB: 20011018
NOVELTY - Forming dopaminergic neurons, comprising contacting neuroprogenitor cells with fibroblast growth factor-8 (FGF-8) and **Sonic hedgehog** (Shh) **polypeptide**, in vitro, encoded by nucleic acid sequences encoding polypeptide comprising a sequence (S1) of 215 or 437 amino acids fully defined in the specification, respectively, is new.

ACTIVITY - Antiparkinsonian; neuroleptic; vulnerary.

MECHANISM OF ACTION - Stimulator of differentiation of neuroprogenitor into dopaminergic neurons (claimed). To examine whether neural progenitor cells utilize the intersecting Shh and FGF-8 signals for their development, ventral hindbrain explants (v4) or mid/hindbrain explants (v3/4) were cultured in the presence of Shh blocking antibody, or the FGF-8 activity blocking reagent respectively, and examined for (5HT) 5-hydroxytryptamine neurons 6 days later. Irrelevant antibodies, or control IgG's (CD4-IgG and FGFR1-IgG), did not prevent normal development of 5HT neurons. However, when similar explants were cultured with FGFR3-IgG or with Shh function blocking antibodies, the development of 5HT neurons was effectively blocked, indicating that the intersection of FGF8 and Shh activity is used as positional information by more than a single cell type.

USE - The method and the composition are useful for forming dopaminergic neurons by stimulating differentiation of neuroprogenitor cells into dopaminergic neurons (claimed), which is useful for treating disorders characterized by abnormalities in the regulation of postural refluxes, movement and reward-associated behaviors including Parkinson's disease, schizophrenia, drug addiction, lesions due to trauma or other illness resulting in Parkinson-like conditions such as resting tremor, rigidity, akinesia and postural abnormality, including akinesia, adipsia, aphagia and sensory neglect.

Dwg.0/14

L6 ANSWER 29 OF 30 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-456723 [49] WPIX
CROSS REFERENCE: 1995-255060 [33]; 2001-079847 [09]; 2001-440859 [47]; 2002-442817 [47]
DOC. NO. CPI: C2001-138112
TITLE: Novel nucleic acid encoding a hedgehog polypeptide, used to produce the polypeptide, which is used to promote proliferation, survival, and/or differentiation of neuronal and mesodermal tissue.
DERWENT CLASS: B04 D16
INVENTOR(S): INGHAM, P W; MCMAHON, A P; TABIN, C J
PATENT ASSIGNEE(S): (HARD) HARVARD COLLEGE; (IMCR) IMPERIAL CANCER RES TECHNOLOGY LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6271363	B1	20010807	(200149)*		118

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6271363	B1	CIP of	US 1993-176427	19931230
		CIP of	US 1994-356060	19941214
		CIP of	US 1995-435093	19950504
		Cont of	US 1995-462386	19950605
			US 1997-954698	19971020

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6271363	B1	CIP of	US 5789543
		CIP of	US 5844079

PRIORITY APPLN. INFO: US 1995-462386 19950605; US 1993-176427 19931230; US 1994-356060 19941214; US 1995-435093 19950504; US 1997-954698 19971020

AN 2001-456723 [49] WPIX

CR 1995-255060 [33]; 2001-079847 [09]; 2001-440859 [47]; 2002-442817 [47]

AB US 6271363 B UPAB: 20020725

NOVELTY - An isolated nucleic acid encoding a hedgehog polypeptide, comprising at least 80 % identity to residues 27-425, 1-336, 25-437, 24-418, 24-475, or 1-312 of a 425, 411, 437, 418, 475, or 312 amino acid sequence (S1), respectively, all fully defined in the specification, is new. The polypeptide binds to naturally occurring patched receptor.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid encoding a **polypeptide** selected from **Sonic hedgehog** and Indian hedgehog **polypeptide**, and comprising a nucleic acid sequence which hybridizes under stringent conditions, including a wash step of 0-2xSSC (saline sodium chloride) at 65 deg. C, to a 1277, 1190, 1281, 1313, 1256, 1425, or 939 nucleotide sequence, all fully defined in the specification; and

(2) an isolated nucleic acid encoding a Sonic or Indian hedgehog protein, comprising at least 80 % identity to (S1).

USE - For producing hedgehog proteins, used for promoting differentiation of, or survival of differentiated, neuronal cells, and for promoting proliferation, survival or differentiation of mesenchymal, endodermal or ectodermal tissue, particularly chondrocytes, or testicular germ line cells (claimed).

Dwg.0/16

L6 ANSWER 30 OF 30 WPIX (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2000-365345 [31] WPIX

DOC. NO. CPI: C2000-110243

TITLE: Polypeptide antagonists of Sonic, Indian and Desert Hedgehog proteins useful for treating cancers, hair loss, nervous system disorders and as diagnostic reagents.

DERWENT CLASS: B04 D16

INVENTOR(S): GARBER, E A; PEPINSKY, B R; RAYHORN, P; WILLIAMS, K
PATENT ASSIGNEE(S): (BIOJ) BIOGEN INC
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000025725	A2	20000511	(200031)*	EN	71
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000021445	A	20000522	(200040)		
EP 1133519	A2	20010919	(200155)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002534060	W	20021015	(200282)		89

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000025725	A2	WO 1999-US25700	19991102
AU 2000021445	A	AU 2000-21445	19991102
EP 1133519	A2	EP 1999-965744	19991102
		WO 1999-US25700	19991102
JP 2002534060	W	WO 1999-US25700	19991102
		JP 2000-579170	19991102

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000021445	A	Based on	WO 200025725
EP 1133519	A2	Based on	WO 200025725
JP 2002534060	W	Based on	WO 200025725

PRIORITY APPLN. INFO: US 1998-106703P 19981102
AN 2000-365345 [31] WPIX
AB WO 200025725 A UPAB: 20000630
NOVELTY - An isolated functional antagonist (Ant) of a hedgehog (HH) polypeptide, which can bind a HH receptor but does not induce a HH-dependent signaling response, is new. Ant comprises one of 6 defined amino acid sequences given in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a DNA sequence (Nuc) encoding Ant;
(2) a vector (Vec) comprising Nuc;
(3) a host cell (Cel) comprising Vec;
(4) a method (METH1) of making Ant, comprising altering an N-terminal Cys-1 residue of a mature HH polypeptide;
(5) a method (METH2) of making Ant, comprising expressing protein from Cel and purifying it; and
(6) a method (METH3) of inhibiting HH-dependent signaling in a subject, comprising administering Ant or Vec.

ACTIVITY - Cytostatic; cerebroprotective; neuroactive.

MECHANISM OF ACTION - Ant is an antagonist of Sonic, Desert and Indian HH polypeptides and can bind to their receptors but cannot induce a HH-dependent signaling response. When bound to the receptor (patched-1), the isolated antagonist either blocks alkaline phosphatase (AP) induction by mature HH protein when tested in an AP assay. The antagonist may also be unable to induce ptc-1 and gli-1 expression (claimed).
No data given.

USE - Ant may be used for treating conditions characterized by over expression or activity of HH polypeptides, such as some basal cell carcinomas, and other human tumors (e.g. breast tumors and medulloblastomas) which have been found to have an oncogenic mutation in the Shh gene and may be treated with Ant. Ant may also be administered to treat neoplastic or hyperlastic transformations of cells of the central nervous system. certain HH proteins may be involved in generation of neuronal tumors, e.g. malignant gliomas, medulloblastomas, neuroectodermal tumors and ependymonas.

The ability of HH proteins to regulate neuronal differentiation during development of the nervous system indicates that Ant may be used to facilitate control of adult neurons with regard to maintenance, functional performance and aging of normal cells, repair and regeneration in lesioned cells, degeneration and premature death. The proteins may also be linked to detectable markers (e.g. fluoroscopically or radiographically opaque substances) and used to image tissues. They may also be bound to substances such as horseradish peroxidase and used as cytochemical stains to allow visualization of areas of HH ligand positive cells on histological sections.

Ant can also be used for inhibiting hair growth in the treatment of trichosis characterized by abnormally rapid or dense growth of hair, e.g. hypertrichosis. Ant can be used to manage hirsutism, a disorder marked by abnormal hairiness. It can also be used for extending the duration of depilation. Ant can be used to inhibit differentiation of epithelial derived tissue and can provide a basis for differentiation therapy for the treatment of hyperlastic and/or neoplastic conditions involving epithelial tissue. For instance, is intended for the treatment of hyperlastic epidermal conditions, such as keratosis, as well as for the treatment of neoplastic epidermal conditions such as those characterized by a high proliferation rate for various skin cancers, as for example basal cell carcinoma or squamous cell carcinoma. Ant can be used for patients undergoing chemo- or radiation-therapies which ordinarily result in hair loss. A hedgehog antagonist will often be cytostatic to epithelial cells, rather than cytotoxic, and such agents can be used to protect hair follicle cells from cytotoxic agents which require progression into S-phase of the cell cycle for efficacy, e.g. radiation-induced death. By inhibiting cell-cycle progression during such therapies, the subject treatment can protect hair follicle cells from death which might otherwise result from activation of cell death programs. Such treatment can provide protection by causing the hair follicle cells to become quiescent. After the therapy has concluded, treatment can also be removed with concomitant relief of the inhibition of follicle cell proliferation.
Dwg.0/4